Rash in a Patient Treated with Pemetrexed for Relapsed Non-small Cell Lung Cancer

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A 66-year-old man was treated with platinum-based induction chemotherapy (three cycles) followed by thoracic radiotherapy for stage IIIB non-small cell lung cancer. Because of the extent of the disease, high-dose thoracic radiotherapy was not feasible, and 36 Gy/3 Gy fractions on the originally involved areas, with a boost of 12 Gy/3 Gy to the region of residual uptake on positron emission tomography scan after chemotherapy was given.

Six months after the initial therapy, the patient experienced anorexia, thoracic pain and cough, based on a local relapse. Administration of the first cycle of second-line pemetrexed (after standard premedication) was complicated 5 days later by a painful, itchy, CTC-NCI grade 2, rash on the thoracic wall (Figure 1). The skin was red, warm, painful, and edematous in an area matching the radiation portal (Figure 2). A skin biopsy revealed a moderate perivascular infiltrate of lymphocytes and eosinophils of the superficial dermis and to a lesser extent of the deeper dermis, compatible with urticarial drug reaction (Figure 3). Treatment with local corticosteroids resulted in complete resolution of the rash within 3 days and the further pemetrexed administration was uneventful.

DISCUSSION

We describe a case of radiation recall dermatitis (RRD) occurring during second-line pemetrexed in a patient treated 6 months after the end of thoracic radiotherapy.

RRD is a rare, well known, but poorly understood phenomenon. After administration of some antineoplastic

FIGURE 1. Clinical image of radiation recall dermatitis in a previously irradiated field.

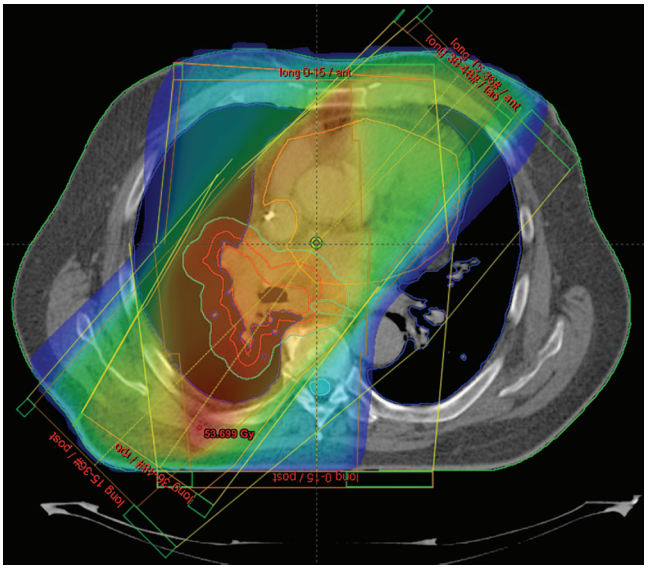

FIGURE 2. Radiation field with the delivered dose of 36 Gy in 3 Gy fractions on the originally involved areas, with a boost of 12 Gy/3Gy to the region of residual uptake on positron emission tomography scan after chemotherapy.

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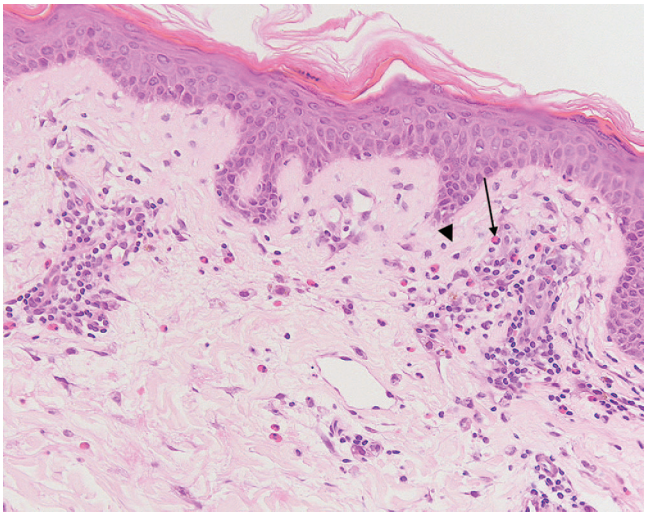

FIGURE 3. Skin biopsy reveals a perivascular infiltrate of lymphocytes (arrow head) and many eosinophils (arrow) in the dermis, the epidermis is normal.

drugs, there is "recalling" of an effect similar to an acute radiation reaction in a previously irradiated field and it is characterized by a mixed nonspecific inflammatory skin reaction. Many hypotheses such as epithelial stem cell inadequacy, local vascular changes, epithelial stem cell sensitivity, or idiosyncratic drug hypersensitivity reaction have been proposed to explain RRD.[1]

RRD usually occurs at first exposure to the responsible drug and should be differentiated from radiosensitization. There is little literature evidence on the incidence of RRD, and most information is on the use of doxorubicin.[1] Factors increasing the risk of development of RRD are a higher dose of radiotherapy, a shorter time interval between radiotherapy and chemotherapy administration, and the specific dose-timing combinations used. Although in one report the median interval between radiotherapy and chemotherapy was reported to be 39.5 days,[2] the time needed between radiotherapy an chemotherapy to avoid RRD is largely unknown. Usually, patients are not rechallenged with the drug, but in cases of further exposure, the reaction is often milder than the initial presentation. When the drug is stopped, skin reactions usually resolve within a few days. The role of steroids or antihistamines in the resolution remain unclear.

To our knowledge, reports of RRD after administration of pemetrexed are very rare. One case was described in a patient with mesothelioma 19 days after radiation therapy (21 Gy/7 Gy fractions) on the thoracoscopy and drainage orifices.[3] Given the short interval, pemetrexed could also have been acting as a radiosensitizing agent some weeks after the radiotherapy. In contrast to our patient, one other report mentioned unsuccessful rechallenge with pemetrexed.[4]

As the use of pemetrexed for second line therapy in non-small cell lung cancer—also after chemoradiation—is increasing, it is important to recognize the pattern of RRD induced by pemetrexed. If there are no good therapeutic alternatives in a certain clinical situation, careful rechallenge may be warranted.

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